OIPE
DEC 30 2005
PATENT & TRADEMARK OFFICE

In re U.S. Patent Application No. 10/750,466
Art Unit: 1626

Dear Mr. Nyeemah Grazier (Examiner of Art Unit: 1626):

Re: Priority Document

1. Reviewing the Notice of Allowability (saying: "None of the Certified Copies of priority documents have been received"), the applicant however had early submitted the Certified copy of Taiwanese patent application (please review PAIR of USPTO).

2. As to the P.2 of Notice of Allowance, Para. II Priority, applicant hereby submits the English translation of Chinese specification of Taiwanese patent application for the above-identified U.S. patent application.

Best regards.

Respectfully submitted:

By: Lee Kwang-Chung
Lee, Kwang-Chung
on: 12/28/2005 12/28/05

Encl. 1. Copy of Notice of Allowability and several Copies of PAIR (PTO).
2. English translation of the corresponding Chinese specification.

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Encl. 1

Notice of Allowability

Application No.	Applicant(s)	
10/750,466	LEE ET AL.	
Examiner	**Art Unit**	
Nyeemah Grazier	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *9/22/05*.
2. ☒ The allowed claim(s) is/are *2-5*.
3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☒ None of the:
   1. ☒ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____.
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
   1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____.
7. ☐ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

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OIPE SEP 22 2004 PATENT & TRADEMARK OFFICE

PTO stamp

Type a plus sign (+) inside this box →

PTO/SB/21 (12-97)
Approved for use through 9/30/00. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/750,466
Filing Date	12/29/2003
First Named Inventor	Lee, Kwang-Chung
Group Art Unit	1614
Examiner Name	
Attorney Docket Number	

Total Number of Pages in This Submission: 13

ENCLOSURES *(check all that apply)*

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment / Response
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [x] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Assignment Papers *(for an Application)*
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition Routing Slip (PTO/SB/69) and Accompanying Petition
- [ ] To Convert a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Small Entity Statement
- [ ] Request for Refund
- [ ] After Allowance Communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Additional Enclosure(s) *(please identify below)*:

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	LEE, KWANG-CHUNG
Signature	Lee, Kwang-Chung
Date	09/14/2004 mailed

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on this date:

Typed or printed name			
Signature		Date	

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be send to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

This is a copy from PAIR/PTO

The following pages are omitted!

中華民國經濟部智慧財產局

INTELLECTUAL PROPERTY OFFICE
MINISTRY OF ECONOMIC AFFAIRS
REPUBLIC OF CHINA

茲證明所附文件，係本局存檔中原申請案的副本，正確無訛，
其申請資料如下 ：

This is to certify that annexed is a true copy from the records of this office of the application as originally filed which is identified hereund

申　請　日：西元 2003 年 02 月 21 日
Application Date

申 請 案 號：092103728
Application No.

申　請　人：中國化學合成工業股份有限公司
Applicant(s)

CERTIFIED COPY OF PRIORITY DOCUMENT

局　　長
Director General

蔡練生

BEST AVAILABLE COPY

發文日期：西元 2004年 9 月 [illegible] 日
Issue Date

發文字號：09320815040
Serial No.

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IAP57

Encl. 2

U.S. Patent No. 10/750,466 Art Unit: 1626

SPECIFICATION

(English Translation of Corresponding Chinese Specification of Taiwanese Patent Application No. 92103728)

Title: Process for Making Mycophenolate Mofetil by Transesterification

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Abstract of the Disclosure:

A process for making mycophenolate mofetil comprising: conducting a catalytic transesterification by reacting a low-carbon alkyl ester of mycophenolic acid with 2-morpholinoethanol [also named as 4-(2-hydroxyethyl) morpholine] to obtain a crude product of mycophenolate mofetil, which is then isolated and purified.

Field: The present invention relates to a process for making mycophenolate mofetil by transesterification.

Background of the Invention (Prior Arts):

U.S. patent 4,753,935 to Peter H. Nelson et al. disclosed a process for making mycophenolate mofetil by first reacting mycophenolic acid (MPA) with thionyl chloride to be an acyl chloride of the MPA, which is then reacted with 2-morpholinoethanol to obtain the mycophenolate mofetil. However, this process may be accompanied with unexpected side reactions, thereby causing serious impurities of the reaction and decreasing the yield of the final product.

U.S. patent 5,247,083 to Martin Knox et al. disclosed a process for making mycophenolate mofetil by refluxing mycophenolic acid with 2-morpholinoethanol in an inert organic solvent even without the use of catalyst. However, the reaction requires a long time period. For example, when the reaction completion was 94.9% by refluxing the reaction mixture at 125~129℃, it already consumed 63 hours. The long reaction time may increase the production cost and may also waste energy when heating the reaction mixture for such a long time period. WO 00/34503 disclosed a process for making mycophenolate mofetil, which however has a defect of high content of impurities.

The present inventor has found the drawbacks of the

conventional process and invented the present process for making mycophenolate mofetil by shortening the reaction time in order to reduce the production cost and improve the product purity.

Summary (content) of the Invention:

The object of the present invention is to provide a process for making mycophenolate mofetil comprising: conducting a catalytic transesterification by reacting a low-carbon alkyl ester of mycophenolic acid with 2-morpholinoethanol [also named as 4-(2-hydroxyethyl) morpholine] to obtain a crude product of mycophenolate mofetil, which is then isolated and purified.

Detailed Description (Example):

For a direct esterification of mycophenolic acid with 2-morpholinoethanol [or named as 4-(2-hydroxyethyl) morpholine], the reaction is difficult and may take a longer reaction time period.

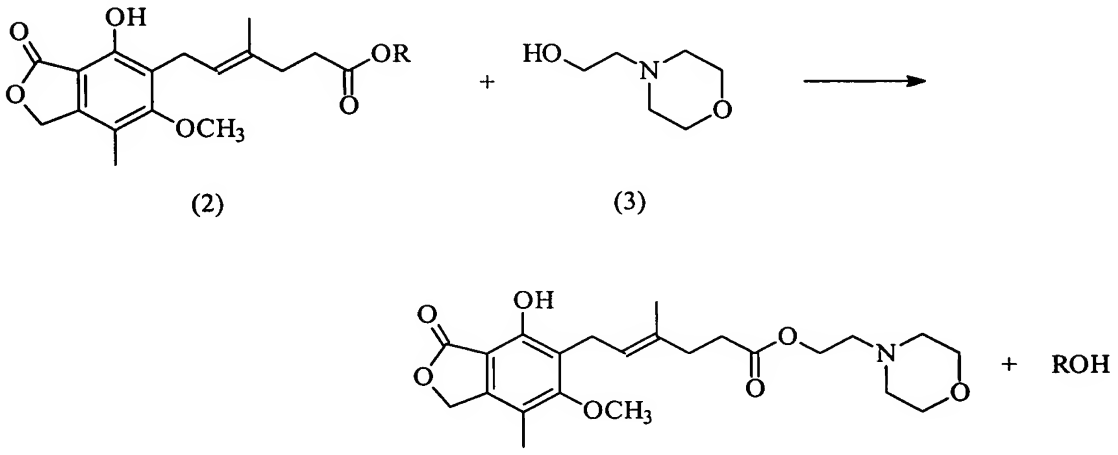
One way may be considered is to first activate the mycophenolic acid (MPA) to be an acyl chloride or acid anhydride of the MPA, and then reacted with 2-morpholinoethanol to produce mycophenolate mofetil (such as taught by U.S. patent 4,753,935). However, the activity may be too strong, thereby accompanying with unexpected side reactions and seriously causing impurities of the product.

Accordingly, the mycophenolic acid may be first esterified, and then reacted with the 2-morpholinoethanol to obtain the

mycophenolate mofetil in accordance with the present invention.

This invention discloses a process by preliminarily conducting an esterification of the mycophenolic acid with an alkyl alcohol of low carbon alkyl group (C_1~C_4) to form a low-carbon alkyl ester, which is then reacted with the 2-morpholinoethanol to obtain the mycophenolate mofetil.

The mycophenolate mofetil (1) of the present invention is obtained by the transesterification of the alkyl mycophenolate (2) with 2-morpholinoethanol (3) in the presence of a catalyst as shown in the following reaction formula:



(2) (3)

(1)

wherein R is an alkyl group selected from the group consisting of methyl, ethyl, propyl and butyl.

After the completion of transesterification, the reaction liquid is added therein with aqueous solution of sodium bicarbonate and ethyl acetate to form a water layer and an organic layer. An aqueous solution of acid such as hydrochloric acid is added into the organic

layer to obtain a hydrochloric acid salt of mycophenolate mofetil which is soluble in water; while the unreacted alkyl mycophenolate (2) is not formed as a hydrochloric acid salt (HCl salt) and is soluble in organic solvent to thereby be easily separated from the HCl salt of mycophenolate mofetil by using an organic solvent to extract and remove the unreacted methyl mycophenolate. Then, an aqueous solution of base such as sodium hydroxide is provided to neutralize the hydrochloric acid to recover the mycophenolate mofetil which is then extracted by an organic solvent.

The catalyst as used in this esterification may be selected from the group consisting of: alkaline metal salt, alkaline earth metal salt, tin oxides and stannous oxides, and may preferably be dibutyl tin oxide, having a catalyst content of 1~200 (weight)%, preferably 5~70 (weight)%, based on the weight of alkyl mycophenolate.

The quantity of 2-morpholinoethanol as used in the transesterificaton may range in 1~20 equivalents, preferably being 1.01~2 equivalents. The esterification reaction temperature is 30~180℃, and preferably being 80~160℃. The organic solvent as used in the reaction may be selected from the group consisting of: benzene, toluene, xylene and the mixture thereof. The reaction may also preclude the use of any organic solvent. The organic solvent used for extraction in this invention may be selected from: benzene, toluene, xylene, ethyl acetate, dichloro-methane, and the mixture

thereof; or any other water-insoluble organic solvent.

The present inventions may be further described in detail with reference to the following example, which is given for description, not to limit the scope of the present invention.

The alkyl mycophenolate may be obtained by reacting the MPA with an alkyl alcohol in the presence of a catalyst overnight (less than 24 hours) to be the alkyl mycophenolate, such as methyl mycophenolate as shown in Example 1.

Example 1

In a reactor, 20.0 grams (59.8 milli moles) methyl mycophenolate, 8.2g (62.6 milli moles) 2-morpholinoethanol, 40 ml toluene and 7.4g (29.8 milli moles) dibutyl tin oxide were added. The reaction mixture (liquid) was heated until an internal temperature 120℃ was reached and the temperature (120℃) was maintained for performing the transesterification reaction for 24 hours.

As checked by HPLC at this moment, there was 1.3% methyl mycophenolate still unreacted. The reaction mixture was cooled to room temperature, added with 100 ml aqueous solution of saturated sodium bicarbonate and 100 ml ethyl acetate, and further agitated for 5 minutes. The insoluble matters were filtered off by celite. A separating funnel was provided for separating the aqueous layer and the organic layer. The aqueous layer was extracted with an organic

solvent, i.e., 100 ml ethyl acetate.

The organic layer combined with the organic solvent, which may contain the mycophenolate mofetil and the unreacted reactants, was added therein with 200 ml water, and further acidified to be an acidic solution by adding 6N hydrochloric acid to obtain a pH value of 1.5. The mycophenolate mofetil was formed as a hydrochloric acid salt to therefore be soluble in the water of the acidic solution while the methyl mycophenolate was not formed as a hydrochloric acid salt, thereby being insoluble is the water. Again, an aqueous layer (containing acid salt of mycophenclate mofetil) layer and an organic layer was thus formed. The aqueous layer was extracted with ethyl acetate (100 ml for each extraction) twice to remove the unreacted methyl mycophenolate.

The aqueous layer containing the hydrochloric acid salt of mycophenolate mofetil was now added therein with 20% sodium hydroxide aqueous solution to be basic (pH = 7.7) to neutralize the hydrochloric acid and recover the mycophenolate mofetil in the aqueous solution.

Ethyl acetate was provided to twice extract the mycophenolate mofetil from the aqueous solution, each extraction using 100 ml of ethyl acetate. The extracts of ethyl acetate were combined as an organic layer and washed with 100 ml aqueous solution of saturated sodium bicarbonate.

The organic layer was purified as being dried by anhydrous

magnesium sulfate, filtered, and evaporated under reduced pressure to obtain 23.2 grams of mycophenolate mofetil, with high purity of 99.9% and high yield of 89.5%.

From the above-mentioned example, it is understood that the present invention may produce mycophenolate mofetil with high purity and high yield in a short reaction time period to thereby reduce the production cost and prevent from wasting of energy to be superior to the prior arts.

I Claim (as amended on Mar. 30, 2004):

1. A process for making mycophenolate mofetil comprising the steps of: (Formula being omitted)

   A. conducting a transesterification by reacting an alkyl mycophenolate with 2-morpholinoethanol in the presence of an organic solvent and a catalyst selected from the group consisting of alkaline metal salt, alkaline earth metal salt, tin oxide and stannous oxide to produce crude mycophenolate mofetil;

   B. adding an acid aqueous solution into said crude mycophenolate mofetil to form an acid salt of mycophenolate mofetil to be soluble in the acid aqueous solution to be separated from the unreacted reactants insoluble in the acid aqueous solution;

   C. basifying the acid aqueous solution to be a base equeous solution by adding a base therein; and

   D. extracting the mycophenolate mefetil from the base aqueous solution by an extracting organic solvent, and purifying the mycophenolate mofetil.

2. A process according to Claim 1, wherein said extracting organic solvent is selected from the group consisting of: benzene, toluene, xylene, ethyl acetate, dichloro methane, and the mixture thereof.

3. A process according to Claim 1, wherein said alkyl mycophenolate is selected from the group consisting of: methyl

mycophenolate, ethyl mycophenolate, propyl mycophenolate and butyl mycophenolate.